REMARKS

Claims 48-62 are pending in the above-identified patent application. Each of these claims was previously presented in Applicants' Preliminary Amendment of April 14, 2004. Claim 54 is amended herein to correct an informality. Claims 53 and 55-62 are withdrawn in accordance with Applicants' previous election.

1. Claim Objections

Claim 54 was subject to objection because of the informality "an" at line 2 should properly be "and". Applicants have corrected claim 54 as requested by the Examiner.

2. Double Patenting

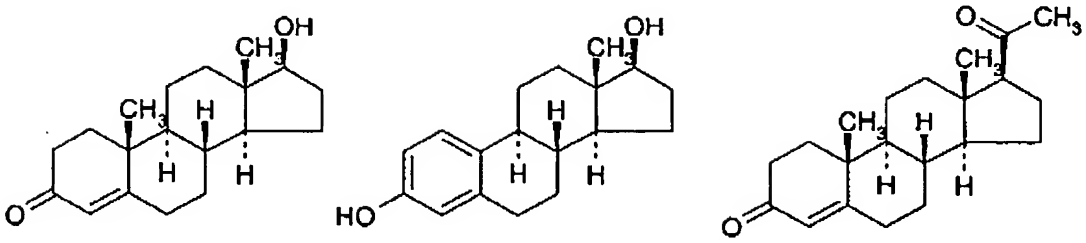
Claims 48-52 and 54 were rejected under the judically created doctrine of obviousness-type double patenting over claims 1-4, 8, 10, 12-14, 18, 20, 27-30, 44-47 56-58, 60 and 64 of US 5,952,362, and over claims 1-10, 17 and 26-39 of US 6,756,395.

a. US 5,952,362

The Examiner stated that US 5,952,362 discloses and claims structural isomers of the compounds claimed in the above-identified application. The Examiner noted in particular that US 5,952,362 discloses compounds having a phenyl ring with a sulfonamide group attached *meta* to the imidazolinylmethyl group, while the instantly claimed compounds include a phenyl ring with with a sulfonamide group attached *para* to the imidazolinylmethyl group. The Examiner stated that nothing unobvious is seen in substituting the known isomer of US 5,952,362 with the presently claimed isomer, since structurally related compounds suggest one another and would be expected to share common properties absent a showing of unexpected results.

Compound Similarity:

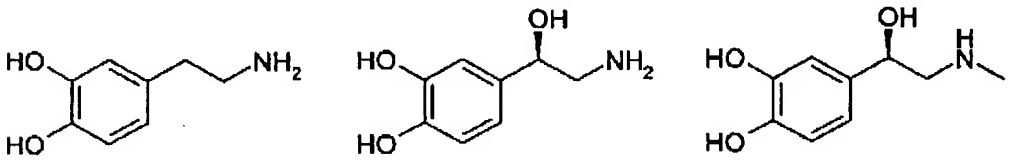
The Applicants note that very small differences in structure can drive very different activities. For example, compare testosterone, progesterone, and estradiol:



Testosterone Estradiol Progesterone

Testosterone and progesterone differ only in the replacement of the D-ring OH with an acetyl group. Testosterone and estradiol differ only in the A-ring methyl group and oxidation state. Despite these minor differences, the compounds have well known divergent activities.

As another example, consider dopamine, epinephrine and norepinephrine:



Dopamine Norepinephrine Epinephrine

Dopamine and norepinephrine (aka noradrenalin) differ by only one OH group, yet dopamine functions as a neurotransmitter in the CNS, while norepinephrine functions as a stress hormone. Norepinephrine and epinephrine (aka adrenalin) differ by only one methyl group, yet epinephrine exhibits strong α_1, α_2, β_1, and β_2 agonist activity, while norepinephrine has weak β_2 agonist activity (with strong α_1, α_2, β_1, and β_2 agonist activity). See, e.g., Remington's Pharmaceutical Sciences, (18th Ed., Mack Pub. Co., 1990), pp. 870-883:

> "Thus, the natural mediator, dopamine, stimulates dopaminergic receptors strongly, β_1-adrenoreceptors moderately, α-adrenoreceptors weakly and β_2-adrenoreceptors negligibly. The predominant sympathetic neurotransmitter, norepinephrine, stimulates α_1- and β_1-adrenoreceptors strongly, α_2-adrenoreceptors moderately, β_2-adrenoreceptors weakly, and dopaminergic receptors negligibly. Epinephrine stimulates all of the α_1-, α_2-, β_1- and β_2-adrenoreceptors strongly and dopaminergic receptors negligibly. Obviously, then, the pharmacodynamic profiles of these three natural sympathomimetics differ considerably from one another." (Remington's at p. 871.)

Accordingly, the Applicants respectfully submit that structurally related compounds do not necessarily share common properties as indicated by the Examiner.

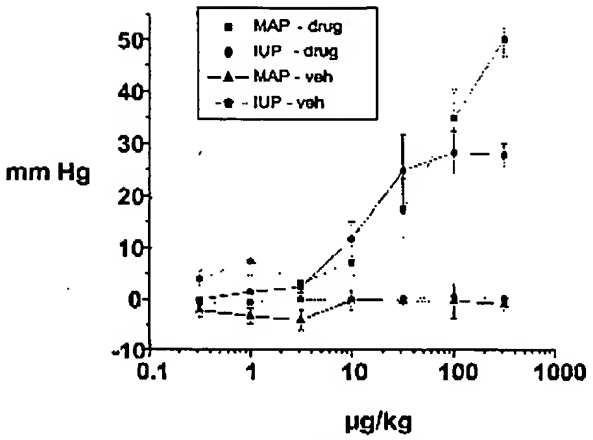
Unexpected Properties

The instantly claimed compounds having a phenyl ring with with a sulfonamide group attached *para* to the imidazolinylmethyl group do in fact have unexpectedly better properties than the corresponding *meta* compounds of US 5,952,362.

Agonists of the alpha 1A adrenoceptor are recognized in the art as being useful for the treatment of genitourinary indications such as various types of incontinence. Modulation of the alpha 1A adrenoceptor can unfortunately result in blood pressure increase and undesirable cardiovascular side effects. A desirable property in alpha 1A agonists is "uroselectivity", i.e., the ability to affect intraurethral pressure (and hence treat incontinence) while avoiding substantial increase in blood pressure.

Both the instant compounds and those of US 5,952,362 have affinity for the alpha 1A adrenoceptor. However, the *para* compounds of the above-identified application have better uroselectivity than the analogous *meta* compounds of US 5,952,362.

Referring first to FIG. 1 and FIG. 2 below, there are shown graphical illustrations of the intraurethral pressure (IUP) versus the mean arterial blood pressure (MAP) for *meta* and *para* analogs determined in an *in vivo* anesthetised rabbit model (see Example 8 of US 6,756,395). The vertical axes represent pressure in millimeters of mercury, and the horizontal axes represent dosage (micrograms of drug per kilograms body mass). The IUP values are represented by circles, while MAP values are represented by squares. The triangles and pentagons represent control solution values for MAP and IUP respectively.



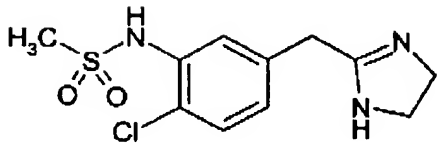
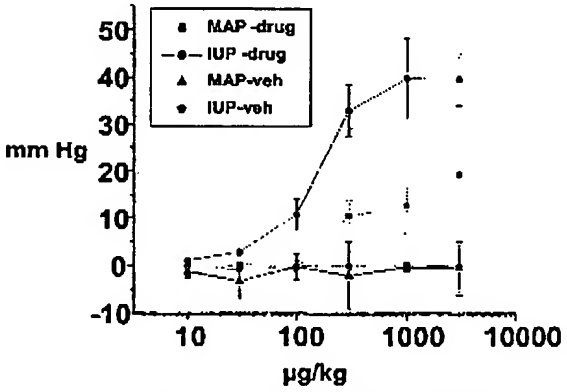


FIG. 1: Intraurethral pressure (IUP) and mean arterial blood pressure (MAP) for N-[2-Chloro-5-(4,5-dihydro-1H-imidazol-2-ylmethyl)-phenyl]-methanesulfonamide (US 5,952,362).

As can be seen in FIG. 1, the mean arterial pressure for the *meta* compound increases commensurately with the intraurethral pressure at lower dosage regimens, and substantiall exceedes the intraurethral pressure at 100 µg/kg and above. The greater increase in arterial blood pressure with respect to intraurethral pressure demonstrates absence of uroselectivity in the *meta* compound.



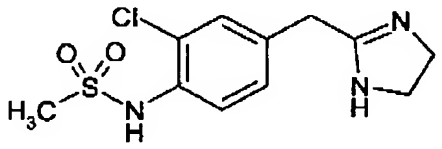


FIG. 2: Intraurethral pressure (IUP) and mean arterial blood pressure (MAP) for N-[2-Chloro-4-(4,5-dihydro-1H-imidazol-2-ylmethyl)-phenyl]-methanesulfonamide

In FIG. 2, the intraurethral pressure exceeds the mean arterial pressure at low dosages, and substantially exceeds the mean arterial pressure at at 100 µg/kg and above.

The greater increase in intraurethral pressure with respect to arterial blood pressure indicates good uroselectivity in the *para* compound.

The Applicants respectfully submit that the *para* compounds of the instant invention have unexpected better uroselectivity than the corresponding *meta* compounds of US 5,952,362. Accordingly, Applicants believe that the compounds claimed in the above identified patent application are patentably distinct from the teachings of US 5,952,362.

b. US 6,756,395

The Applicants will submit a terminal disclaimer (37 CFR §1.321(c)) to disclaim any patent term which extends beyond that of US 6,756,395. Applicants will submit the terminal disclaimer upon resolution of the other outstanding claim rejections.

2. Rejection Under 35 USC §103

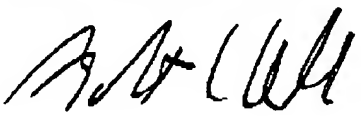
Claims 48-52 and 54 were rejected under 35 USC §103 as unpatentable over Cournoyer et al., US 5,952,362. In view of the unexpected uroselectivity of the instantly claimed *para* compounds over the *meta* compounds disclosed by Cournoyer et al. as described above, Applicants respectfully believe that claims 48-52 and 54 are patentable over US 5,952,362.

CONCLUSION

The Applicants respectfully believe that all claims pending in the above-identified case will be in condition for allowance upon Applicants' submission of a terminal disclaimer as noted above. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-354-7540.

Please charge the fee for extension of time (37 CFR§1.17(a)(5)) to deposit account No. 18-1700.

Respectfully submitted,



Roche Palo Alto
Patent Department, MS A2/250
Palo Alto, CA 94301
Phone: (650) 354-7540

Robert C. Hall
Reg. No. 39,209
Attorney for Applicants

October 20, 2005